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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/529,342	07/27/2000	DAVID J. CLARKE	39-206	8022

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EXAMINER	
YANG, NELSON C	
ART UNIT	**PAPER NUMBER**
1641	

DATE MAILED: 08/25/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/529,342	CLARKE ET AL.	
	Examiner	Art Unit	
	Nelson Yang	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *42-68* is/are pending in the application.

4a) Of the above claim(s) *43,44,53,62,63,67 and 68* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *42,45-52,54-61 and 64-66* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 April 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

1. Applicant's election with traverse of cytolytic peptides noncovalently attached to an outer lipid layer, GALA and N, Myristic GALA, and change in pH, in the reply filed on May 22, 2006 is acknowledged. The traversal is on the ground(s) that no reasons for the election of species was given. This is not found persuasive as the reasons for the election of species were stated in the restriction requirement mailed March 22, 2006. More specifically, the Office indicated the reason behind restricting the cytolytic peptides was that "the species appear to refer to different types of cytolytic peptides, that would function differently to modulate pore formation" and that "the species are different peptides, that respond to different environmental triggers, rendering the search for all the species burdensome" and with respect to the metabolic signal, "the species are different metabolic changes that would affect different cytolytic peptides differently". Therefore, applicant's arguments have not been found persuasive.

2. The restriction requirement with respect to claims 54, 57 has been withdrawn since there was found not to be a burden of search involved in searching the additional species of dyes and substrates.

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 42, 45-52, 54-61, 64-66 are currently under examination.

4. Claims 43-44, 53, 62-63, 67-68 have been withdrawn.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 65-66 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

7. With respect to claims 65-66, it is unclear what the limitations that "the pH is above 6" and that "the pH is above 7" are referring to, the pH prior to the change or the pH after the change. Currently, it is assumed that the pH is in reference to the pH prior to the change.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 42, 45-49, 51, 52, 54, 55, 58, 61, 64-66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Meers et al [US 6,087,325] in view of Parente et al [Parente et al, Mechanism of leakage of phospholipid vesicle contents induced by the peptide GALA, 1990, Biochemistry, 29, 8720-8728].

10. With respect to claims 42, 51, 52, Meers et al teach a method comprising the steps of treating a sample with lipid vesicle particles incorporating a peptide that modulates the permeability of the particles in response to a predetermined metabolic signal from a targeted cell type (column 1, line 60 – column 2, line 20). Meers et al further teach that the liposomes of this invention can incorporate a species activated on modulation of permeability (column 9, lines 25-

48), comprising one or more "bioactive agents," which are compounds or compositions of matter having biological, including therapeutic or diagnostic, activity in animals (column 9, lines 25-48), and which include dyes and radiolabels (column 9, lines 40-50) and fluorescent labels (column 20, lines 51-62). The particles can be used to deliver diagnostically effective amounts of diagnostic agents into the cells of a mammal afflicted with a disease, disorder, or condition (column 10, lines 59-65). Meers et al further teach monitoring the fluorescence (column 20, lines 60-62). Meers et al do not teach the use of liposomes comprising peptides that are cytolytic peptides such GALA or KALA.

Parente et al, however, do teach the use of liposomes GALA (p.8720, col.1, lines 12-26), and further teaches that GALA assembles to form a pore or channel (lysing the lipid vesicle), leakage is rapid and complete (p.8726, col. 2, lines 4-17). Furthermore, one of ordinary skill in the art would have had a reasonable expectation of success in substituting the peptide of Meers et al with the GALA of Parente et al, as Meers et al disclose a higher level of liposome binding to cells at pH 4.0 than at pH 7.4 (col. 20, lines 51-67), while Parente et al disclose that 100% leakage occurs at pH 5, while leakage is halted at pH 7 (p.8724, col.1, lines 1-20). Since the amino acid sequence of GALA and N, Myristic GALA is essentially the same, with similar functions and pH sensitivities, GALA would be functionally equivalent to N, Myristic GALA and therefore it would be obvious to utilize GALA or N, Myristic GALA, in order permit rapid and complete leakage when GALA lyses the lipid vesicles.

Therefore it would be obvious to utilize liposomes comprising a cytolytic peptide such as GALA or N, Myristic GALA in the method of Meers et al, in order to modulate the permeability

of the particles in response to a predetermined metabolic signal from a targeted cell type, as taught by Parente et al, in order permit rapid and complete leakage.

11. With respect to claim 45, Parente et al. teach the use of GALA (p.8720, col.1, lines 12-26), and further teaches that once GALA assembles to form a pore or channel (lysing the lipid vesicle).

12. With respect to claims 46-47, Meers et al teach that the liposomes can comprise a targeting moiety such as antibodies that can direct the liposomes to specific sites within the body of a mammal (column 8, lines 3-20).

13. With respect to claims 48-49, Meers et al teach that liposomes can comprise glycoprotein streptavidin (second binding moiety) which can be used to link proteins (first binding moiety) (column 9, lines 20-25). Aggregation would occur when multiple liposomes bind to the same cell of interest.

14. With respect to claims 54-55, Meers et al teach that the species can be a dye or an enzyme (column 9, lines 25-48).

15. With respect to claims 58 and 61, Meers et al teach that the liposome can be used for diagnostic activity in animals (column 9, lines 25-29).

16. With respect to claims 64-66, Parente et al teach that leakage of the vesicles would occur as the pH is changed from a pH of 7.3 to pH of 5 (p.8723, col.2, lines 21-26, fig. 2B). Meers et al further teach that binding of liposomes to cells of interest increase at changes of pH to around 4 (col. 20, lines 51-67).

17. Claim 50 is rejected under 35 U.S.C. 103(a) as being unpatentable over Meers et al [US 6,339,069 B1] in view of Parente et al [Parente et al, Mechanism of leakage of phospholipid

vesicle contents induced by the peptide GALA, 1990, Biochemistry, 29, 8720-8728] and in light of Li et al [US 5,512,294].

With respect to claims 50, Meers et al teach a method comprising the steps of treating a sample with lipid vesicle particles incorporating a cytolytic peptide that modulates the permeability of the particles in response to a predetermined metabolic signal from a targeted cell type (column 1, line 60 – column 2, line 20) and further incorporating a species activated on modulation of permeability (column 9, lines 25-48). Meers et al further teach that liposomes can comprise glycoprotein streptavidin (second binding moiety) which can be used to link proteins (first binding moiety) (column 9, lines 20-25). Meers et al do not specifically teach using biotin as the second binding moiety.

Li et al do, however, demonstrate that teach liposomes where avidin is used to bind proteins such as antibodies, the antibodies are attached by the biotin-avidin biotinylated antibody sandwich (fig.16, column 9, lines 65-67). One of ordinary skill in the art would therefore realize to attach proteins to streptavidin, they would need to biotinylate the proteins.

18. Claims 56-57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Meers et al [US 6,087,325] in view of Parente et al [Parente et al, Mechanism of leakage of phospholipid vesicle contents induced by the peptide GALA, 1990, Biochemistry, 29, 8720-8728] and further in view of Levinson et al [US 6,020,142].

With respect to claims 56-57, Meers et al teach a method comprising the steps of treating a sample with lipid vesicle particles incorporating a cytolytic peptide that modulates the permeability of the particles in response to a predetermined metabolic signal from a targeted cell type (column 1, line 60 – column 2, line 20) and further incorporating a species activated on

modulation of permeability (column 9, lines 25-48). Meers et al teach that the species can be a dye or an enzyme (column 9, lines 25-48). Meers et al do not teach that the species is a substrate for an enzyme or is glucose oxidase.

Levinson et al, however, teach the use of a delivery complex such as liposomes (column 3, lines 5-12) for delivering enzymes and substrates such as glucose oxidase (column 25, lines 40-42) in order to label RATH gene peptide-specific antibodies. This is important as the RATH1.1 gene product has been demonstrated to act as a mediator of signal transduction events, and and the detection of compounds which modulate the RATH gene product would allow for the diagnostic evaluation, prognosis, and treatment of immune disorders involving T cell activation (column 1, lines 29-62).

Therefore one of ordinary skill in the art would have been motivated to have the liposomes deliver enzymes and substrates such as glucose oxidase, as suggested by Levinson et al, in the method of Meers et al and Parente et al, to in order to study specific cells such as T cells, such that the diagnostic evaluation, prognosis, and treatment of immune disorders involving T cell activation is possible.

19. Claim 59 is rejected under 35 U.S.C. 103(a) as being unpatentable over Meers et al [US 6,087,325] in view of Parente et al [Parente et al, Mechanism of leakage of phospholipid vesicle contents induced by the peptide GALA, 1990, Biochemistry, 29, 8720-8728] and further in view of Robinson et al [US 5,994,149].

Meers et al teach a method comprising the steps of treating a sample with lipid vesicle particles incorporating a cytolytic peptide that modulates the permeability of the particles in response to a predetermined metabolic signal from a targeted cell type (column 1, line 60 –

column 2, line 20) and further incorporating a species activated on modulation of permeability (column 9, lines 25-48). Meers et al further teach that the liposome can be used for diagnostic activity in animals (column 9, lines 25-29). Meers et al do not teach the detection of pathogenic cells in foodstuffs.

Robinson et al, however, do teach the analysis of foodstuffs for pathogenic cells using liposomes (column 4, lines 19-24). Robinson et al further teach that it would be desirable to have a test kit that would eliminate operator error, and have a predictably accurate and reproducible rate of identification of pathogenic fungi, yeasts and molds (column 1, lines 16-45).

Therefore it would be obvious to teach the detection of pathogenic cells in foodstuffs, as taught by Robinson et al, in the method of Meers et al and Parente et al, in order to have a test kit that would eliminate operator error, and have a predictably accurate and reproducible rate of identification of pathogenic fungi, yeasts and molds.

20. Claim 60 is rejected under 35 U.S.C. 103(a) as being unpatentable over Meers et al [US 6,087,325] in view of Parente et al [Parente et al, Mechanism of leakage of phospholipid vesicle contents induced by the peptide GALA, 1990, Biochemistry, 29, 8720-8728] and further in view of Blondin et al [US 4,808,517].

Meers et al teach a method comprising the steps of treating a sample with lipid vesicle particles incorporating a cytolytic peptide that modulates the permeability of the particles in response to a predetermined metabolic signal from a targeted cell type (column 1, line 60 – column 2, line 20) and further incorporating a species activated on modulation of permeability (column 9, lines 25-48). Meers et al further teach that the liposome can be used for diagnostic

activity in animals (column 9, lines 25-29). Meers et al do not teach the detection of pathogenic cells in foodstuffs. Meerss et al do not teach the detection of pathogenic cells in water samples.

Blondin et al, however, do teach a method of using of lipid vesicles (column 4, lines 9-24) for the detection of toxins in water samples (column 8, lines 20-32) that is economical and efficient and can be quickly and easily performed (column 2, lines 64-68).

Therefore it would be obvious to use the method of Meers et al and Parente et al to analyze water samples for pathogens as taught by Blondin et al, in order to detect toxins economically, efficiently, quickly and easily.

Response to Arguments

21. Applicant's arguments with respect to claims 42, 45-52, 54-61, 64-66 have been considered but are moot in view of the new ground(s) of rejection. The following arguments, however, have been addressed.

Applicant's argument on p. 8 that Meers et al does not disclose a method of detecting target cells is not found persuasive, as Meers et al refers to the use of the liposomes for diagnostic activity several times throughout the reference, and further disclose examples involving detecting fluorescence from the liposomes as that contact cells of interest (column 20, lines 30-45).

With respect to applicant's arguments regarding Parente et al, applicant argues on p. 9 that the peptides only associate with lipid membranes when they are in the lytic, pH activated state, the Office cannot find where in the reference applicant found support for this argument. While it is agreed that at a pH activated state, more GALA becomes incorporated into the

membrane to produce GALA-induced leakage, Parente et al also teach that to induce the same extent of leakage at pH 6, the peptide concentration must be increased over 10 fold, and at 7.5, the extent of leakage never becomes greater than 30% (p.8724, col.2). Therefore, one can assume that GALA does associate with the lipid membranes when at neutral pH, abeit to a smaller extent. Furthermore, applicant never recites that GALA is pre-associated with the lipid vesicles, merely that GALA is incorporated into the vesicles, which Parente et al do teach. It is also noted that applicant has not recited how GALA is pre-associated with the lipid vesicles, which could simply involve incubating the vesicles with GALA, as Parente et al teach (p. 8724, col. 2). In particular, it is unclear if applicant is arguing that GALA would not have worked as a cytolytic peptide in the method of Meers et al, or if there are additional limitations which have not been recited by applicant in order for GALA to work as the cytolytic peptide. Applicant's states that pH activation shifted markedly to within a typical physiological range of just less than neutral (see p. 13, step. b), but fails to indicate what causes this shift (which could be attributed to GALA concentration, as discussed by Parente et al (p.8724, col.2)).

It is also noted that the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985). Since Parente et al teach that GALA assembles to form a pore or channel (lysing the lipid vesicle), leakage is rapid and complete (p.8726, col. 2, lines 4-17), one of ordinary skill in the art would have been motivated to use GALA with liposomes in the method of Meers et al.

For these reasons, applicant's arguments have not been found persuasive.

Conclusion

22. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nelson Yang whose telephone number is (571) 272-0826. The examiner can normally be reached on 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long V. Le can be reached on (571)272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

23. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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